

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 2

PATENT NO. : 7,449,470

APPLICATION NO.: 10/574,436

ISSUE DATE : November 11, 2008

INVENTOR(S) : Lisa Chung Wai Chang, Adriaan P. Ijzerman, Johannes Brusse

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column	Line	Error	Correct to Read
15	37	desired product. ^1H NMR δ (DMSO- d_6):	desired product. ^1H NMR δ (DMSO- d_6):
16	41	($\text{C}_{18}\text{H}_{15}\text{N}_3\text{O} \cdot 0.5.0.\text{EtOH}$), C, H, N.	($\text{C}_{18}\text{H}_{15}\text{N}_3\text{O} \cdot 0.5.0.\text{EtOH}$), C, H, N.
17	33	6H, $J=7.31$ Hz, $\text{CH}(\text{CH}_2\text{CH}_3)_2$ ppm.	6H, $J=7.31$ Hz, $\text{CH}(\text{CH}_2\text{CH}_3)_2$ ppm.
18	52	13 $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O} \cdot 25\text{H}_2\text{O}$ Calc.	13 $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O} \cdot 0.25\text{H}_2\text{O}$ Calc.
18	54	14 $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O} \cdot 0.5\text{EtOH}$.	14 $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O} \cdot 0.5\text{EtOH}$.
18	58	16 $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O} \cdot 0.14\text{H}_2\text{O}$	16 $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O} \cdot 0.14\text{H}_2\text{O}$
18	60	17 $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O} \cdot 0.1\text{H}_2\text{O}$	17 $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O} \cdot 0.1\text{H}_2\text{O}$
18	64	19 $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O} \cdot 0.1\text{H}_2\text{O}$	19 $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O} \cdot 0.1\text{H}_2\text{O}$
19	10	23 $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O} \cdot 0.01\text{H}_2\text{O}$	23 $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O} \cdot 0.01\text{H}_2\text{O}$
19	12	24 $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O} \cdot 0.04\text{H}_2\text{O}$	24 $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O} \cdot 0.04\text{H}_2\text{O}$

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Column	Line	Error	Correct to Read
19	14	25 $C_{23}H_{23}N_3O \bullet 0.15H_2O$	25 $C_{23}H_{23}N_3O \cdot 0.15H_2O$
19	43	substuents are varied.	substituents are varied.
20	65	Potent A Adenosine Receptor Antagonists.	Potent A ₃ Adenosine Receptor Antagonists.

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(12) **United States Patent**
Chang et al.

(10) **Patent No.:** **US 7,449,470 B2**
(45) **Date of Patent:** **Nov. 11, 2008**

- (54) **SUBSTITUTED PYRIMIDINES AS LIGANDS OF ADENOSINE RECEPTORS**
- (75) Inventors: **Lisa Chung Wai Chang**, Sydney (AU);
Adriaan P. Ijzerman, Haarlem (NL);
Johannes Brussee, Rijnsburg (NL)
- (73) Assignee: **Universiteit Leiden**, Leiden (NL)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 70 days.

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- § 371 (c)(1),
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- (30) **Foreign Application Priority Data**
- Oct. 3, 2003 (GB) 0323137.0

- (51) **Int. Cl.**
- C07D 239/42** (2006.01)
A61K 31/505 (2006.01)
A61P 9/00 (2006.01)
A61P 11/00 (2006.01)
A61P 25/00 (2006.01)
A61P 35/00 (2006.01)

- (52) **U.S. Cl.** **514/256; 544/326; 544/329**
- (58) **Field of Classification Search** **544/326, 544/329; 514/275, 256**
- See application file for complete search history.

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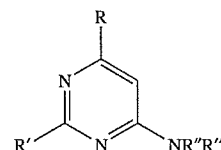
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(57) ABSTRACT

The invention provides a compound of formula (I) wherein R and R' are selected from hydrogen, alkyl, alkenyl, alkynyl, or aryl; R" and R''' are selected from hydrogen, acyl, thio-acyl, seleno-acyl, alkyl, alkenyl, alkynyl, or aryl; or a pharmaceutically acceptable salt thereof, to interact with the adenosine receptors in the beneficial treatment and/or prevention of a (dis)order arising from the said receptors. The invention further provides pharmaceutical compositions comprising said compounds. The invention also relates to the use of said compositions for treating an/or preventing a variety of diseases.



5 Claims, No Drawings

Chemistry—General

Chemicals and Solvents All reagents were obtained from commercial sources and all solvents were of an analytical grade.

Chromatography Thin-layer chromatography (TLC) was carried out using Merck silica gel plastic backed F₂₅₄ plates, visualised under UV (254 nm).

Instruments and Analysis Elemental analyses were performed for C,H,N (Leiden Institute of Chemistry, Leiden University, The Netherlands). ¹H and ¹³C NMR spectra were recorded on a Bruker AC 200 (¹H NMR, 200MHz; ¹³C NMR, 50.29 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm (δ) relative to this. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Mass Spectra were measured on a Finnigan MAT TSQ-70 spectrometer equipped with an electrospray interface for ESI experiments. Spectra were collected by constant infusion of the analyte dissolved in methanol. ESI is a soft ionisation technique resulting in protonated, sodiated species in positive ionisation mode and deprotonated species in the negative ionisation mode.

Synthetic Procedures

2,6-Diphenyl-3H-pyrimidin-4-one (10)⁷

Benzamidinium hydrochloride (3.9 g, 24.9 mmol) was dissolved in a minimal amount of H₂O (10 mL), to this was added sodium hydroxide pellets (1.0 g, 24.9 mmol, 1 eq.) dissolved in H₂O (2 mL), followed by ethylbenzoate (4.53 mL, 26.1 mmol, 1.05 eq.). Ethanol was then added until a clear solution was obtained. The reaction mixture was then allowed to stir at room temperature overnight yielding a thick suspension, which was then filtered to give a white solid. After washing with diethyl ether to remove unreacted/excess β-ketoester the solid was dried in vacuo to give 57% of the desired product (¹H NMR δ (DMSO-d₆): 8.31-8.18 (m, 5H, Ar), 7.60-7.54 (m, 5H, Ar), 6.92 (s, 1H, Ar).

→ ¹H

4-Chloro-2,6-diphenyl-pyrimidine (11)⁸

Phosphorous oxychloride (9.30 mL, 99.8 mmol, 7.5 eq.) was added dropwise to 2,6-diphenyl-3H-pyrimidin-4-one (10) (3.3 g, 13.3 mmol) in a vigorous reaction. To this mixture was added slowly phosphorous pentachloride (2.77 g, 13.3 mmol, 1 eq.) and the reaction mixture was stirred at reflux for 3 hours. The reaction mixture was then quenched by pouring into ice-water, and extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with water and brine, dried (MgSO₄) and then concentrated to give a yellow solid. This was recrystallised from hot ethanol to give fine white needles (65%). ¹H NMR δ (CDCl₃): 8.60-8.18 (m, 5H, Ar), 7.63 (s, 1H, Ar), 7.51-7.57 (m, 5H, Ar).

2,6-Diphenyl-pyrimidin-4-ylamine (12)

Ethanol (50 mL) was saturated with NH_{3(g)} at 0° C. and added to 4-chloro-2,6-diphenyl-pyrimidine (11) (2.30 g, 8.63 mmol) in a sealed vessel. This was then stirred at 140° C. for 24 h. Upon cooling and concentrating, the residues were extracted with hot chloroform (3×50 mL) and the solvent evaporated in vacuo. The crude product was purified by column chromatography on SiO₂ eluting with CH₂Cl₂ to give an off-white solid (80%). ¹H NMR δ (DMSO-d₆): 8.47-8.42 (m, 2H, Ar), 8.16-8.13 (m, 2H, Ar), 7.57-7.5 (m, 6H, Ar), 7.02 (br s, 2H, NH₂), 6.88 (s, 1H, Ar).

General Procedure for the Preparation of 4-Amido-2,6-diphenylpyrimidines (13-25)

To a solution of 4-amino-2,6-diphenylpyrimidine (0.202 mmol, 1 eq.) in 1,4-dioxane (5 mL) was added triethylamine (0.223 mmol, 1.1 eq.), followed by the appropriate acid chloride (0.304 mmol, 1.5 eq.). This was then stirred at reflux until no starting material was visible by TLC. Upon completion, the reaction mixture was separated between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was further extracted with ethyl acetate (2×20 mL) and the combined organics washed with water and brine. After drying over MgSO₄ and evaporation under reduced pressure, the crude product was purified by column chromatography, eluting with a petroleum ether-ethyl acetate or a dichloromethane-methanol solvent system. Recrystallisation with ethanol or petroleum ether-ethyl acetate gave the corresponding amide in crystalline form.

N-(2,6-Diphenyl-pyrimidin-4-yl)-benzamide (13).

Yield 48%; white solid; mp 120-123° C.; ¹H NMR δ (CDCl₃): 8.78 (bs, 1H, N—H), 8.72 (s, 1H, pyrimidine-H), 8.58-8.54 (m, 2H, phenyl-H), 8.34-8.29 (m, 2H, phenyl-H), 7.99-7.96 (m, 2H, phenyl-H), 7.64-7.48 (m, 9H, phenyl-H). ¹³C-NMR δ (CDCl₃): 166.2, 165.9, 164.0, 158.4, 137.3, 137.1, 133.4, 132.6, 130.8, 130.7, 128.9, 128.7, 128.3, 128.1, 127.4, 127.2, 103.3. MS (ES⁺): 351.57, 373.55 Da. Anal. (C₂₃H₁₇N₃O. 0.25H₂O) C, H, N.

N-(2,6-Diphenyl-pyrimidin-4-yl)-acetamide (14).

Yield 43%; white solid; mp 140° C.; ¹H NMR δ (CDCl₃): 8.54-8.49 (m, 3H, phenyl-H+ pyrimidinyl-H) 8.45 (s, 1H, N—H), 7.55-7.49 (m, 6H, phenyl-H), 2.20 (s, 3H, CH₃)ppm. ¹³C-NMR δ (CDCl₃): 165.9, 158.1, 154.3, 140.7, 130.74, 130.68, 128.7, 128.4, 128.0, 127.4, 103.0, 35.7ppm. MS (ES⁺): 289.89 Da. Anal. (C₁₈H₁₅N₃O. 0.50EtOH) C, H, N.

N-(2,6-Diphenyl-pyrimidin-4-yl)-propionamide (15).

Yield 77%; white solid; mp 125-126° C.; ¹H-NMR δ (CDCl₃): 8.58 (s, 1H, pyrimidinyl-H), 8.55-8.50 (m, 2H, phenyl-H), 8.36 (bs, 1H, NH), 8.30-8.25 (m, 2H, phenyl-H), 7.54-7.49 (m, 6H, phenyl-H), 2.41(q, 2H, J=7.3 Hz, CH₂CH₃), 1.23 (t, 2H, —CH₂CH₃)ppm. ¹³C-NMR δ (CDCl₃): 173.2, 165.8, 163.9, 137.3, 137.0, 130.7, 128.7, 128.0, 127.4, 121.5, 103.1, 30.7, 8.87ppm. MS (ES⁺): 303.8 Da. Anal. calc. for C₁₉H₁₇N₃O (C 75.23; H 5.65; N 13.85) found (C 75.32; H 6.23; N 14.04)%.

N-(2,6-Diphenyl-pyrimidin-4-yl)-butyramide (16).

Yield 53%; white solid; mp.102-103° C. ¹H-NMR δ (CDCl₃): 8.60 (bs, 2H, pyrimidine-H+NH), 8.56-8.51 (m, 2H, phenyl-H), 8.31-8.26 (m, 2H, phenyl-H), 7.45-7.50 (m, 6H, phenyl-H), 2.29 (t, 2H, J=7.48 Hz, CH₂CH₂CH₃), 1.71 (sextet, 2H, J=7.39 Hz, CH₂CH₂CH₃), 0.95 (t, 3H, J=7.30 Hz, CH₂CH₂CH₃)ppm. ¹³C-NMR δ (CDCl₃): 172.9, 165.8, 163.8, 158.5, 137.4, 137.0, 130.8, 130.7, 128.6, 128.4, 128.1, 127.3, 103.3, 39.2, 18.3, 13.5 ppm. MS (ES⁺): 317.87 Da. Anal. (C₂₀H₁₉N₃O. 0.14H₂O) C, H, N.

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N-(2,6-Diphenyl-pyrimidin-4-yl)-isobutyramide (17).

Yield 48%; white solid; mp 116-117° C. ¹H-NMR δ (CDCl₃): 8.59 (s, 1H, pyrimidine-H), 8.55-8.50 (m, 2H, phenyl-H), 8.30-8.25 (m, 2H, phenyl-H), 8.05 (bs, 1H, NH), 7.54-7.49 (m, 6H, phenyl-H), 2.64 (septet, 1H, J=6.85 Hz, CH(CH₃)₂), 1.33 (d, 6H, J=6.94 Hz, CH(CH₃)₂)ppm. ¹³C-NMR δ (CDCl₃): 176.5, 165.8, 158.3, 137.4, 137.1, 130.7, 128.7, 128.4, 128.0, 127.4, 103.4, 36.8, 19.2, 19.1 ppm. MS (ES⁺): 317.94, 634.75 Da. Anal. (C₂₀H₁₉N₃O.0.1H₂O).

N-(2,6-Diphenyl-pyrimidin-4-yl)-3-methyl-butyramide (18).

Yield 52%, white solid. mp. 127° C. ¹H-NMR δ (CDCl₃): 8.59 (s, 1H, pyrimidinyl-H), 8.56-8.51 (m, 2H, phenyl-H), 8.35 (bs, 1H, NH), 8.31-8.26 (m, 2H, phenyl-H), 7.56-7.49 (m, 6H, phenyl-H), 2.25-2.24 (m, 3H, CH₂CH(CH₃)₂), 1.02-0.99 (d, 6H, CH₂CH(CH₃)₂)ppm. ¹³C-NMR δ (CDCl₃): 172.1, 165.9, 158.2, 137.4, 137.1, 130.7, 130.6, 128.6, 128.4, 128.0, 127.4, 113.5, 103.2, 46.8, 25.8, 22.3 ppm. MS (ES⁺): 331.8 Da. Anal. (C₂₁H₂₁N₃O).

N-(2,6-Diphenyl-pyrimidin-4-yl)-2-ethyl-butyramide (19).

Yield 58%, white solid. mp. 137-138° C. ¹H-NMR δ (CDCl₃): 8.64 (s, 1H, pyrimidine-H), 8.55-8.50 (m, 2H, phenyl-H), 8.31-8.26 (m, 2H, phenyl-H), 8.09 (bs, 1H, NH), 7.54-7.49 (m, 6H, phenyl-H), 2.23-2.11 (m, 1H, CH(CH₂CH₃)₂), 1.86-1.56 (m, 4H, CH(CH₂CH₃)₂), 0.99 (t, 6H, J=7.31 Hz, CH(CH₂CH₃)₂)ppm. ¹³C-NMR δ (CDCl₃): 175.8, 165.9, 158.3, 130.8, 130.7, 128.7, 128.4, 128.1, 127.4, 121.6, 103.2, 52.2, 25.5, 11.8 ppm. MS (ES⁺): 345.86, 690.56 Da. Anal. (C₂₂H₂₃N₃O.0.1H₂O).

N-(2,6-Diphenyl-pyrimidin-4-yl)-2-methyl-butyramide (20).

Yield 89%, white solid. mp.: 102° C. ¹H-NMR δ (CDCl₃): 8.71 (br s, 1H, N-H), 8.67 (s, 1H, pyrimidinyl-H), 8.59-8.54 (m, 2H, aromatic-H), 8.33-8.28 (m, 2H, aromatic-H), 7.53-7.50 (m, 6H, aromatic-H), 2.29-2.19 (m, 1H, CH), 1.82-1.86 (m, 1H, 0.5*CH₂), 1.55-1.41 (m, 1H, 0.5*CH₂), 1.16 (d, J=6.58Hz, 3H, CH₃), 0.90 (t, J=7.30 Hz, 3H, CH₃) ppm. ¹³C-NMR δ (CDCl₃): 176.4, 165.9, 163.9, 158.5, 137.4, 137.1, 130.8, 130.7, 128.7, 128.4, 128.1, 127.4, 103.3, 44.0, 27.0, 16.9, 11.6 ppm. MS (ES⁺): 331.8 (MH⁺) Da. Anal. (C₂₁H₂₁N₃O).

N-(2,6-Diphenyl-pyrimidin-4-yl)-2,2-dimethyl-propionamide (21).

Yield 66%, white solid. mp. 52° C. ¹H-NMR δ (CDCl₃): 8.63 (s, 1H, pyrimidinyl-H), 8.58-8.51 (m, 2H, phenyl-H), 8.30-8.27 (m, 2H, phenyl-H), 8.21 (s, 1H, N—H), 7.54-7.51 (m, 6H, phenyl-H), 1.40 (s, 9H, CH₃)ppm. ¹³C-NMR δ (CDCl₃): 178.0, 165.8, 163.8, 158.4, 137.3, 137.1, 130.7, 130.6, 128.6, 128.3, 128.1, 127.4, 103.2, 40.0, 27.2 ppm. MS (ES⁺): 331.92 Da. Anal. (C₂₁H₂₁N₃O).

N-(2,6-Diphenyl-pyrimidin-4-yl)-3,3-dimethyl-butyramide (22).

Yield 62%, white solid. mp.: 134° C. ¹H-NMR δ (CDCl₃): 8.73 (br s, 1H, N—H), 8.64 (s, 1H, pyrimidinyl-H), 8.55-8.50

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(m, 2H, aromatic-H), 8.32-8.27 (m, 2H, aromatic-H), 7.54-7.49 (m, 11H, aromatic-H), 2.20 (s, 2H, CH₂), 1.08 (s, 9H, 3*CH₃) ppm. ¹³C-NMR δ (CDCl₃): 171.7, 165.9, 163.9, 158.4, 137.4, 137.1, 130.8, 130.7, 128.7, 128.4, 128.2, 127.4, 103.2, 51.0, 31.2, 30.0 ppm. MS (ES⁺): 367.6 (MNa⁺), 345.9 (MH⁺) Da. Anal. (C₂₂H₂₃N₃O).

Cyclobutanecarboxylic acid
(2,6-diphenyl-pyrimidin-4-yl)-amide (23).

Yield 90%, white solid. mp.: 121-122° C. ¹H-NMR δ (CDCl₃): 8.62 (s, 1H, pyrimidinyl-H), 8.56-8.51 (m, 2H, phenyl-H), 8.32-8.27 (m, 3H, phenyl-H+N—H), 7.54-7.48 (m, 6H, phenyl-H), 3.13 (pentet, 1H, —CHCH₂CH₂CH₂—), 2.45-1.90 (m, 6H, —CHCH₂CH₂CH₂—)ppm. ¹³C-NMR δ (CDCl₃): 174.6, 165.8, 163.9, 158.4, 137.1, 130.7, 128.7, 128.4, 128.0, 127.4, 103.2, 86.9, 40.7, 24.9, 17.9 ppm. MS (ES⁺): 329.7 Da. Anal. (C₂₁H₁₉N₃O.0.01H₂O).

Cyclopentanecarboxylic acid
(2,6-diphenyl-pyrimidin-4-yl)-amide (24).

Yield 69%, white solid. mp.: 126.5-127° C. ¹H-NMR δ (CDCl₃): 8.60 (s, 1H, pyrimidinyl-H), 8.56-8.51 (m, 2H, phenyl-H), 8.32-8.26 (m, 3H, phenyl-H+N—H), 7.53-7.50 (m, 6H, phenyl-H), 2.77-2.65 (m, 1H, —CHCH₂CH₂CH₂CH₂—), 1.98-1.60 (m, 8H, —CHCH₂CH₂CH₂CH₂—)ppm. ¹³C-NMR δ (CDCl₃): 175.9, 165.8, 158.4, 137.4, 137.1, 130.7, 130.6, 128.7, 128.4, 128.0, 127.4, 103.2, 46.8, 30.2, 25.9 ppm. MS (ES⁺): 343.7 Da. Anal. (C₂₂H₂₁N₃O.0.04H₂O).

Cyclohexanecarboxylic acid
(2,6-diphenyl-pyrimidin-4-yl)-amide (25).

Yield 87%, white solid. mp.: 142-143° C. ¹H-NMR δ (CDCl₃): 8.60 (s, 1H, pyrimidinyl-H), 8.57-8.52 (m, 2H, phenyl-H), 8.34 (bs, 1H, NH), 8.30-8.25 (m, 2H, phenyl-H), 7.53-7.49 (m, 6H, phenyl-H), 2.31-2.18 (m, 1H, —CHCH₂CH₂CH₂CH₂CH₂—), 1.97-1.30 (m, 10H, —CHCH₂CH₂CH₂CH₂CH₂—)ppm. ¹³C-NMR δ (CDCl₃): 175.7, 165.8, 163.8, 158.4, 137.1, 130.7, 130.6, 128.6, 128.3, 127.3, 113.6, 103.2, 46.4, 29.2, 25.3 ppm. MS (ES⁺): 357.7, 358.7 Da. Anal. (C₂₃H₂₃N₃O.0.15H₂O).

TABLE 1

		Elemental Analysis		
Compound		Elemental Analysis		
No.	Molecular formula	C %	H %	N %
13	C ₂₃ H ₁₇ N ₃ O-0.25H ₂ O Calc. Found 0.625	77.61	4.81	11.80
14	C ₁₈ H ₁₅ N ₃ O-0.95EtOH 0.0.5	77.61	5.07	11.88
		74.13	5.18	14.41
15	C ₁₉ H ₁₇ N ₃ O	74.06	5.57	14.40
		75.23	5.65	13.85
16	C ₂₀ H ₁₉ N ₃ O-0.14H ₂ O 0.0.14	75.32	6.23	14.04
		75.10	6.07	13.14
17	C ₂₀ H ₁₉ N ₃ O-0.14H ₂ O 0.0.1	75.09	6.29	13.28
		75.26	6.00	13.16
18	C ₂₁ H ₂₁ N ₃ O	75.24	6.20	13.47
		76.13	6.34	12.69
19	C ₂₂ H ₂₃ N ₃ O-0.1H ₂ O 0.0.1	76.34	6.71	12.88
		76.10	6.68	12.10
20	C ₂₁ H ₂₁ N ₃ O	76.02	6.87	12.35
		76.13	6.34	12.69
21	C ₂₁ H ₂₁ N ₃ O	76.25	6.72	12.92
		76.11	6.39	12.68
		75.79	6.62	12.79

TABLE 1-continued

Compound	Molecular formula	Elemental Analysis		
		C %	H %	N %
22	C ₂₂ H ₂₃ N ₃ O	76.49	6.71	12.16
23	C ₂₁ H ₁₉ N ₃ O-0.01H ₂ O 0.0.01	76.77	6.81	12.56
		76.53	5.81	12.75
24	C ₂₂ H ₂₁ N ₃ O-0.04H ₂ O 0.0.04	76.16	6.21	12.94
		76.78	6.15	12.21
25	C ₂₃ H ₂₃ N ₃ O-0.15H ₂ O 0.0.15	76.40	6.56	12.31
		76.70	6.44	11.67
		76.47	6.84	11.85

Biology

A primary function of certain cell surface receptors is to recognise appropriate ligands. Accordingly, we performed radioligand binding studies to establish the degree to which the compound binds to the receptor.

Radioligand Binding Studies [³H]DPCPX was purchased from Amersham. All compounds made were tested in radioligand binding assays to determine their affinities at the human adenosine A₁ receptor. The affinities at the A₁ receptors were determined on CHO cells expressing the human receptors, using [³H]DPCPX as the radioligand according to a previously described method.⁹

Data Analysis Competition binding data were fit to a single-site binding model and plotted using the software package Prism (Graph Pad, San Diego, Calif., USA). The Cheng-Prusoff equation $K_i = IC_{50} / (1 + [I]/K_d)$ was used to calculate K_i values, where K_i is the affinity constant for the competing ligand, [I] is the concentration of the free radioligand, and K_d is the affinity constant for the radioligand.

Structure Activity Relationships

In Table 2 results of the radioligand binding assays at the A₁ receptor are displayed, the substituents are defined herein above and below with reference to the compound of general formula (II). The reported literature focuses generally on bi- and tri-cyclic heterocycles as the core structure about which substituents are varied. This monocyclic core with the 2,4,6-trisubstitution pattern has surprising efficacy at the adenosine A₁ receptor, as can be seen in Table 2. The compounds shown in Table 2 were also tested at the adenosine A_{2A} and A₃ receptors and were shown to be generally selective for the adenosine A₁ receptor.

TABLE 2



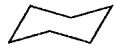
Radioligand Binding Assay		
Comp	R	A ₁ ^a
13	Ph	671 ± 113
14	CH ₃	37.5 ± 8.1
15	CH ₂ CH ₃	9.50 ± 4.6
16	(CH ₂) ₂ CH ₃	17.6 ± 5.3
17	CH(CH ₃) ₂	11.1 ± 6.2
18	CH ₂ CH(CH ₃) ₂	14.8 ± 2.7
19	CH(CH ₃ CH ₃) ₂	6.35 ± 0.4
20	CH(CH ₃)CH ₂ CH ₃	2.22 ± 1.1
21	C(CH ₃) ₃	27.7 ± 6.2
22	CH ₂ C(CH ₃) ₃	8.75 ± 4.1
23		6.49 ± 2.2

TABLE 2-continued

Radioligand Binding Assay		
Comp	R	A ₁ ^a
24		2.14 ± 0.07
25		15.5 ± 8.4

^aDisplacement of specific [³H]DPCPX binding in CHO cells expressing human adenosine A₁ receptors. K_i (nM) ± SEM (n = 3).

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substituents